

REMARKS

Applicant respectfully requests reconsideration. Claims 50, 52, 53, 55-57, 59, 60, 62-64, 66-70 and 72-86 were previously pending in this application. Claim 59 has been amended herein. New claims 97-102 are added. As a result, claims 50, 52, 53, 55-57, 59, 60, 62-64, 66-70 72-86 and 97-102 are pending for examination with claims 50, 57, 64, 70, 77, and 82 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claim 59 has been rejected under U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which application regards as the invention. Claim 59 has been amended to correct the dependency. It is believed that the rejection is overcome.

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In response to Applicant's arguments the Examiner has asserted that the rejection is maintained because 1) although the specification discloses many nucleic acids, the nucleic acids that are effective for treating viral infection are not disclosed, 2) only a single mention of HBV occurs in the specification, and 3) that "functional characteristics" are a factor for determining written description. Applicant will address each of these below.

1) It is stated that although the specification discloses many nucleic acids, the nucleic acids that are effective for treating viral infection are not disclosed. Applicants disagree. Applicant has taught that the minimal element for modulating an immune response and treating viral infection is an unmethylated CpG dinucleotide. It is now believed that CpG oligonucleotides act through a common cellular receptor, TLR9. It is believed that CpG oligonucleotides are recognized by TLR9 and that this leads to the promotion of an immune response in which a Th1 response is favored. Hemmi et al., Nature, 2002, vol. 408, page 740 was one of the first publications to describe the role of TLR9 in activation of the immune response by CpG oligonucleotides. Briefly, Hemmi et al.

describes studies in a TLR9 knockout mouse. The CpG mediated Th1 immune response was abolished in these mice, confirming the role of TLR9 in CpG mediated signaling.

2.) It is stated in the office action that applicant only mentions HBV once in the specification. The Examiner concludes that one of skill in the art would not be convinced that Applicant was in possession of the invention due to this one recitation. (Office Action pages 5-6).

Viruses and viral infections, including HBV, were well known to those of ordinary skill in the art at the time of the invention. One of skill in the art seeing the mention of HBV, in the one place that it was mentioned, would immediately understand what HBV infection is. Further mention of HBV in different places in the specification would not have advanced the understanding of one skilled in the art. Additionally there was no requirement for Applicant to include background information on HBV which is well known to those of skill in the art. The fact that HBV is only named in one place in the specification is not relevant to whether one skilled in the art would have understood that the inventors had possession of the invention because viruses are well known in the art.

3.) On page 6 of the office action the Examiner addresses Applicant's argument related to "functional characteristics." The Examiner states that functional characteristics are one factor to consider. Applicant agrees with this. The point Applicant was attempting to make in the prior response is that a disclosure of functional characteristics is not required for enablement. It is simply an example of factors to look for. The MPEP states:

"Whether the specification shows that applicant was in possession of the claimed invention *is not a single, simple determination, but rather is a factual determination reached by considering a number of factors*. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406." (emphasis added).

Applicant addresses each of these factors listed in the above MPEP section separately:

1. level of skill and knowledge in the art: The level of skill in the art is high. A skilled artisan in the field is an individual with a PhD or MD in the biological sciences, such as immunology or virology.

2. partial structure: The basic structure of oligonucleotides was well known in the art at the time of the invention. Applicant has described a core component of a set of oligonucleotides that is understood to those of ordinary skill in the art, an unmethylated CpG dinucleotide. Applicant discovered that inclusion of an unmethylated CpG dinucleotide in an oligonucleotide resulted in a drug that was capable of causing the body to mount a natural response against invading organisms. It is taught in the specification that the immune reaction to CpG oligonucleotides is believed to be representative of a natural host response to bacterial infection (paragraph 0116-118). It was recognized by the inventors that the immune response to CpG motifs is similar to that which occurs in a subject with bacterial infection. Unmethylated CpG motifs are present in bacterial DNA in much higher amounts than in vertebrate DNA. By using synthetic oligonucleotides having unmethylated CpG motifs one can mimic bacterial DNA and stimulate a host response to bacterial infection, thus adding to the natural host response and providing a highly effective response to an invading organism. Numerous publications following Applicant's priority date have described the unmethylated CpG dinucleotide as the essential component of immune stimulatory oligonucleotides. Also it has now been described in publications that CpG oligonucleotides act through a common cellular receptor, TLR9. It is believed that CpG oligonucleotides are recognized by TLR9 and that this leads to the promotion of an immune response in which a Th1 response is favored. It is this common mechanism that unifies the resultant immune response produced by CpG oligonucleotides.

3. physical and/or chemical properties: The specification describes the physical and chemical properties of this class of oligonucleotides. The specification provides a description of the genus of immunostimulatory CpG oligonucleotides, including preferred species and subgenus. (See paragraphs 0052-0061). The specification also provides representative species of these oligonucleotides, as well as data demonstrating their

immunostimulatory activity. (See for example Tables 1-14 and the Examples and accompanying descriptions). The specification also describes backbone modifications (See paragraphs 0067-0069). Thus, the physical and chemical properties of the oligonucleotides are described in the specification.

4. functional characteristics alone or coupled with a known or disclosed correlation between structure and function: The specification describes a class of oligonucleotides having an unmethylated CpG dinucleotide that have a particular function, that is they stimulate an immune response and that this response is useful for the treatment of viral infection. As described above, it is now known that CpG oligonucleotides act through a common receptor, TLR9 to promote this immune response. Applicant describes this functional property associated with CpG oligonucleotides throughout the specification and at least in paragraph 0014 and 0021.

5. method of making the claimed invention: Methods of making the claimed oligonucleotides are known in the art and are described in the specification. (See paragraph 0137).

Applicants have satisfied each of the factors outlined in this section of the MPEP.

The Examiner has not met the burden of making a *prima facie* case as to why the specification does not adequately support the claims such that it lacks written description. MPEP 2163.04 teaches that:

“The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). *A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption.* See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.” (emphasis added).

A preponderance of evidence supporting the assertion that a person skilled in the art would not believe that applicant had possession of the claimed invention has not been presented. In fact no evidence has been presented in either Office Action of record to establish that one of skill in the art would not recognize in applicant's disclosure a description of the invention defined by the claims. The rejection consists only of statements directed to the fact that the specification includes a limited description of HBV and does not show a specific nucleotide useful in a working example of the use of a CpG oligonucleotide in the treatment of HBV infection. A lack of a specific working example for the treatment of HBV infection is not sufficient evidence to establish that one of skill in the art would not recognize Applicant as being in possession of the claimed invention.

The Examiner has suggested in the office action that Applicants assertion that CpG oligonucleotide's ability to induce an immune response as described in the specification is not adequate to demonstrate to one skilled in the art that Applicant had possession of the invention. Applicant's disagree. One skilled in the art would recognize the utility of treating HBV infection based on the disclosure and data provided in the instant patent application. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFN γ (Figure 15) as well as other cytokines.

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In response to Applicant's arguments the Examiner has asserted that the rejection is maintained because 1) Applicant has not provided working examples on the treatment of a viral infection and the examples directed to immune modulation are not sufficient to demonstrate the effectiveness of immune modulation, 2) the cytokine art is useful for establishing unpredictability because Applicant relies on cytokine levels to and establish written description and enablement 3) that CpG ODN are unpredictable across species. Applicant will address each of these below.

1) According to the Examiner Applicant has not provided working examples on the treatment of a viral infection and the examples directed to immune modulation are not sufficient to

demonstrate the effectiveness of immune modulation. The Examiner asserts that the working examples presented in the application are not commensurate in scope with the claimed invention and do not sufficiently provide a correlation between CpG and its use in treating and preventing viral infectivity.

Applicants disagree and maintain their assertion that, while not actually having treated subjects infected with HBV with the CpG oligonucleotides of the claimed invention, said oligonucleotides induce a pattern of immunostimulation that is consistent with the treatment of viral infection. Further, one of skill in the art, at the time of the invention, would have believed that based on the data and teachings of the specification that one of skill in the art could use CpG oligonucleotides to treat HBV infection.

Applicants disagree with the notion that no facts have been provided to substantiate Applicant's assertion that the observed pattern of immunostimulation is consistent with the treatment of viral infection. Despite having provided such evidence during earlier stages of the prosecution Applicants hereby submit additional evidence to show that the state of the art at the time the invention was made would have allowed a person of ordinary skill in the art to draw conclusions from the observed pattern of immunostimulation as to the utility of the CpG oligonucleotides to treat viral infection, including HBV.

Applicants have demonstrated that oligonucleotides containing unmethylated CpG motifs are effective in inducing a pattern of immune stimulation that is consistent with the treatment of viral infection. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFN γ (Figure 15) as well as other cytokines. On page 53 of the application it states that "in response to unmethylated CpG containing nucleic acid molecules, an increased number of spleen cells secrete IL-6, IL-12, IFN-gamma, IFN-alpha, IFN-beta, IL-1, IL-3, IL-10, TNF-alpha, TNF-beta, GM-CSF, RANTES, and probably others. The increased IL-6 expression was found to occur in B-cells, CD4⁺ T cells and monocytic cells". This is shown in Examples 2, 3, 4, 11, and Figures 6, 11 and 15. One skilled in the art would recognize that a drug useful for boosting such cytokines would be useful in the treatment of HBV.

The results obtained by Applicants *in vitro* and *in vivo* (i.e. immune stimulation) are correlated with the specific condition claimed (i.e. viral infection and in particular HBV infection) and the Examiner has failed to provide sufficient evidence that the model does not correlate.

The Examiner has not made a *prima facie* case of lack of enablement. MPEP § 2164.04 teaches that in "order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35USC 112 first paragraph, *unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support*. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370." (emphasis added). In the instant case the Patent Office has not provided a sufficient reason to doubt the objective truth of the statements made in the specification. The only doubt raised related to the lack of an *in vivo* test of viral infection and the references cited in support of the unpredictability. Applicant previously addressed each of these references. Thus, a *prima facie* rejection has not been made.

2) The Examiner has responded to Applicant's arguments and stated that the cytokine art is useful for establishing unpredictability because Applicant relies on cytokine levels to and establish written description and enablement. Applicants disagree. Administration of a cytokine is very

different than administering a natural component that induces the body to produce a balanced immune response. A single cytokine may bring benefit to a subject but it may throw off the balance of other factors leading to problems and side effects. CpG oligonucleotides when administered to the body mimic bacterial infection and cause the body to develop a natural immune response. The issues of enablement for a CpG oligonucleotide and a cytokine are not the same. The specific points were addressed in response to the last office action.

3) The examiner has also asserted that the use of CpG ODN across species is unpredictable. Applicant disagrees. Although mouse are different than humans this is true in the context of all drug testing. However, the scientific community still relies on mouse studies for a significant amount of research.

Further, Applicants reiterate all prior arguments that were not addressed in the instant office action. In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and have provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat or prevent a viral infection. Based on the teachings in the specification one skilled in the art would have predicted that CpG is capable of treating viral infection. Numerous references, including those cited by the Examiner, have shown that CpG oligonucleotides can overcome infection, suggesting that CpG ODN is effective in treating viral infection. Therefore, the amount of experimentation required to practice the invention is not undue.

Accordingly, withdrawal of the rejection of claims 42-43, 47-51, 55-58 and 62-71 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Double Patenting Rejection

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 97

of copending Application No. 10/613524. Applicant notes that claim 97 of US 10/613524 has been withdrawn pursuant to a restriction requirement and will be canceled. It is believed that the rejection is moot.

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 59-61 of copending Application No. 11/255100. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 40 of copending Application No. 10/613524. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47, 52, 57, 72 and 74 of copending Application No. 11/071836.

Applicants elect to defer substantive rebuttal of the rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application Nos. 11/255100, 10/613524 and 11/071836 until such time as the cited applications are allowed. Applicant understands that procedurally, in accordance with Section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner in each case until the "provisional" double patenting rejection is the only rejection remaining in one of the applications. The patent office should allow the earlier filed application. the instant application to issue as a patent.

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-33 of copending Application No. 10/987146. Applicants elect to defer substantive rebuttal of the rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application No. 10/987146 until such time as the cited application is allowed. Applicant understands that procedurally, in accordance with Section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner in each case until the "provisional" double patenting rejection is the only rejection remaining in one of the

applications. Should the pending claims in the cited co-pending Applications be found to be allowable and Applicants are unable to overcome any remaining provisional obvious-type double patenting rejections in the instant case, Applicants will consider filing a terminal disclaimer in the instant case to overcome the rejection.

Applicant notes that each of US 10/627,331, 10/382,822, 10/306,522, 10/627,413, 10/187,489, 10/649,584, 10/788,199, 10/788,191, 10/987,146 is co-owned and includes claims directed to various methods of treating viral infection. Applicant has noticed that the double patenting rejections between the cases are inconsistent and would like to ensure that the Examiner is aware of the co-pending commonly owned patent applications as well as the discrepancy in double patenting rejections.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

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